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Chiral Discrimination of Cryptochiral Saturated Quaternary and Tertiary Hydrocarbons by Asymmetric Autocatalysis

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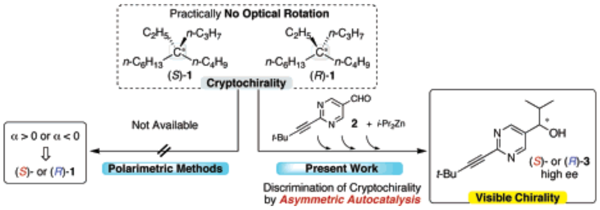
Chirality plays a central role in chemical, biological, pharmaceutical, and material sciences. The fundamental prerequisite of a study on chirality is the availability of a method to discriminate between enantiomeric forms (i.e., chiral discrimination). Thus, the discovery of the rotation of plane polarized light initiated the study of chiral compounds possessing optical activity.[1] Although significant progress in chiral discrimination has been achieved in the intervening decades,[2] there remains a class of compounds whose chiral discrimination has been very difficult to establish, or has not been possible at all. Chiral saturated hydrocarbons form a class of compounds whose chiral discrimination has often been very difficult.[1] Unlike other functionalized compounds, chiral saturated hydrocarbons do not bear heteroatom(s), π-electrons, or chromophores, and therefore, the difference between the four substituents on the asymmetric carbon atom is very small.

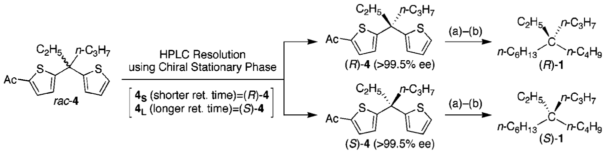
An example of a compound whose chiral discrimination poses the utmost difficulty is a saturated *quaternary* hydrocarbon bearing similar substituents on the asymmetric carbon atom, with a representative example being 5-ethyl-5-propylundecane **1**, that is, (*n*-butyl)ethyl(*n*-hexyl)(*n*-propyl)methane,[3] a naturally occurring compound found in *Phaseolus vulgaris* L., a kind of bean.[4] Wynberg reported that the enantiomer of **1** exhibits practically no optical rotation ($|\alpha| < 0.001$) between 280 and 580 nm. The enantiomeric **1** is a *chiral*, but to all intents an *optically inactive*, compound. The exceedingly small chiroptical character of **1**, below the level of detection, is attributed to the very small differences between the four alkyl substituents; that is, the difference in the number of carbon atoms is only 1 or 2, and due to the fact that chiral **1** bears the same four methylene groups adjacent to the quaternary asymmetric carbon atom. To the best of our knowledge, the chirality of **1** has not been discriminated using any contemporary method. Mislow called such hidden chirality “cryptochirality” and referred to the corresponding measurement as the “operational null.”[5] It should be noted that for the simple empirical formula of a saturated hydrocarbon, C_nH_{2n+2}, the number of *chiral* isomers, that is, isomers possessing asymmetric carbon atom(s), is twice that of the *achiral* isomers for decane ($n = 10$) and ca. 95% of isomers are chiral for tetradecane ($n = 14$).[6]

We report here the first chiral discrimination of a saturated quaternary hydrocarbon **1** by using asymmetric autocatalysis and the determination of absolute configuration of **1**. In the presence of chiral alkane **1**, pyrimidine-5-carbaldehyde **2** was reacted with diisopropylzinc (i-Pr_2Zn). We postulated that cryptochiral alkane **1** would tip the balance of chirality of the initially formed isopropyl zinc alkoxide of pyrimidyl alkanol **3**, and after the asymmetric autocatalysis with amplification of the chirality, alkanol **3** with an amplified enantiomeric excess correlated with the absolute configuration of alkane **1** would be formed (Scheme 1). Thus, by detecting the absolute configuration of **3**, we can determine the absolute configuration of cryptochiral **1**.

Scheme 1. Discrimination of Cryptochiral Quaternary Alkane with No Detectable Optical Rotation Using Asymmetric Autocatalysis



Scheme 2 . Preparation of the Enantiomers of **1**[a]



[a] Reagents and conditions: (a) N_2H_4, KOH (93%); (b) Ni_2B, MeOH/THF then Raney Ni (W7) (66%).

The enantiomers of alkane **1** were prepared as shown in Scheme 2. Racemic **4** was resolved using HPLC with a chiral stationary phase (Chiralpak AD-H) into enantiomers $\mathbf{4_S}$ (**4** with a shorter retention time) and $\mathbf{4_L}$ (**4** with a longer retention time) with >99.5% ee. The absolute configurations of $\mathbf{4_S}$ and $\mathbf{4_L}$ were determined to be *R* and *S*, respectively, from X-ray crystallographic analysis of 2,4-dinitrophenylhydrazone derived from $\mathbf{4_S}$. Deoxygenative reduction, desulfurization, and hydrogenation of (*R*)- and (*S*)-**4** gave the chiral quaternary hydrocarbons (*R*)- and (*S*)-**1**, respectively.

We found that the chirality of the saturated quaternary hydrocarbon **1** was successfully discriminated using asymmetric autocatalysis. Table 1 shows the results of asymmetric autocatalysis triggered by cryptochiral **1**. The asymmetric autocatalysis initiated by chiral alkane (*R*)-**1** using 2-alkynylpyrimidine-5-carbaldehyde **2** and i-Pr_2Zn afforded (*S*)-pyrimidyl alkanol **3** with a 97% ee and a 93% yield (run 1). In contrast, asymmetric autocatalysis in the presence of (*S*)-**1** afforded (*R*)-pyrimidyl alkanol **3** with a 94% ee in a 91% yield (run 2). These stereochemical correlations were found to be reproducible (runs 3 and 4, respectively). It should be noted that alkane **1**, which had been derived independently from the precursor **4** with lower enantiomeric excess (80−91% ee), also gave the same correlation of the stereochemistry of 5-pyrimidyl alkanol **3** with a high enantiomeric excess (runs 5−8).

The chiral quaternary alkane **1** does not have any π-electrons or a heteroatom. Thus, the present chiral discrimination may involve the CH−π interactions between the CH group of chiral hydrocarbon **1** and the π-electrons of the pyrimidine-5-carbaldehyde **2**. This CH−π interaction[10] may be used to discriminate between the *re* and *si* enantiofaces of aldehyde **2** because alkane **1** is chiral, and the subsequent attack of i-Pr_2Zn to aldehyde **2** from one of the enantiofaces of the aldehyde preferentially forms the isopropyl zinc alkoxide of pyrimidyl alkanol with an absolute configuration

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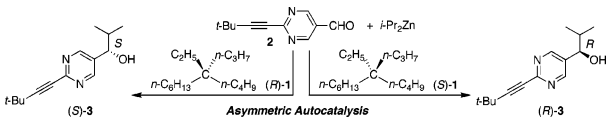
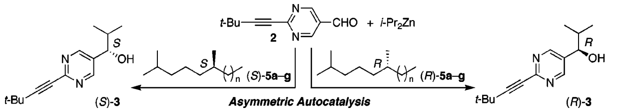
Table 1. Chiral Discrimination of the Cryptochiral Quaternary Alkane **1** Using the Asymmetric Autocatalysis

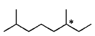
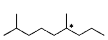
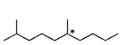
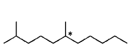
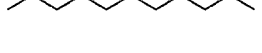
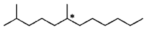
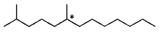


run^a	Chiral Alkane **1**^{b} config	5-Pyrimidyl alkanol **3** yield (%)^c	ee (%)^d	config
1	*R*^{e}	93	97	*S*
2	*S*^{e}	91	94	*R*
3	*R*^{e}	89	93	*S*
4	*S*^{e}	91	95	*R*
5	*R*^{f}	93	97	*S*
6	*S*^{f}	94	97	*R*
7	*R*^{f}	97	91	*S*
8	*S*^{f}	93	95	*R*

[a] Molar ratio of **1**:**2**:*i*-Pr$_2$Zn = 0.77:0.85:1.83. [b] The purity of **1** was checked by GC analysis to be >99%. [c] Isolated yields. [d] Enantiomeric excess was determined by HPLC using a chiral stationary phase (csp). [e] Enantiomeric excesses of precursor **4** were determined to be >99.5% by HPLC using a csp. [f] Enantiomeric excesses of **4** were 80−91%.

Table 2. Chiral Discrimination of Saturated Tertiary Alkanes **5a**−**g**



run^a	chiral alkane **5**^{b}			5-pyrimidyl alkanol **3**		
			config	yield (%)^c	ee (%)^d	config
1		**5a**	*S*	96	92	*S*
2		**5a**	*R*	97	95	*R*
3		**5b**	*S*	94	98	*S*
4		**5b**	*R*	96	96	*R*
5		**5c**	*S*	98	98	*S*
6		**5c**	*R*	89	95	*R*
7		**5d**	*S*	99	97	*S*
8		**5d**	*R*	98	98	*R*
9		**5e**	*S*	93	95	*S*
10		**5e**	*R*	95	99	*R*
11		**5f**	S	95	97	S
12		**5f**	*R*	97	97	*R*
13		**5g**	*S*	99	98	*S*
14		**5g**	R	98	97	*R*

[a] Molar ratio of **5**:**2**:*i*-Pr$_2$Zn = 0.15:1.325:2.65. [b] (*S*)- and (*R*)-**5a**−**g** were synthesized from (*R*)-(+)-citronellal with ca. 82−84% ee and (*S*)-(−)-citronellal with >99.5% ee, respectively. The purity of **5a**−**g** was checked by GC to be >99%. [c] Isolated yields. [d] See Table 1, footnote d.

corresponding to that of chiral hydrocarbon **1**. Once the isopropyl zinc alkoxide of pyrimidyl alkanol with a tiny enantioenrichment is formed, then the chirality amplifies during the asymmetric autocatalysis.

In addition, we examined the chiral discrimination of chiral saturated tertiary alkanes, and the results are shown in Table 2. The chiral alkanes **5a**−**g**[11] were used as the chiral initiators of asymmetric autocatalysis. When (*S*)-2,6-dimethyloctane **5a** was used as the chiral initiator, (*S*)-pyrimidyl alkanol **3** with a 92% ee was obtained in a 96% yield (run 1). On the other hand, (*R*)-**5a** induced the production of (*R*)-**3** with a 95% ee in a 97% yield (run 2). Asymmetric autocatalysis in the presence of (*S*)- and (*R*)-alkane **5b** gave (*S*)- and (*R*)-alkanol **3** with a 98 and 96% ee, respectively (runs 3 and 4). In a similar manner, (*S*)- and (*R*)-alkanes **5c**−**g** induced the formation of (*S*)- and (*R*)-alkanol **3** with the same sense of stereochemistry, respectively (runs 5−14). Two of the substituents of hydrocarbons **5a**−**g** were fixed as 4-methylpentyl and methyl groups, and the length of the primary alkyl substituents was elongated successively by one carbon atom (runs 1−14). As shown in Table 2, (*S*)- and (*R*)-2,6-dimethyltridecane **5f** (entries 11 and 12) and (*S*)- and (*R*)-2,6-dimethyltetradecane **5g** (entries 13 and 14), whose number of carbon atoms in the primary alkyl substituents was larger than that of the 4-methylpentyl group, gave (*S*)- and (*R*)-alkanol **3** with a 97−98% ee in a high yield. These results show that the branched 4-methylpentyl group served as a more stereodemanding substituent than the primary heptyl and octyl substituents with more carbon atoms.

In summary, we have demonstrated that asymmetric autocatalysis is a significant method for discriminating the cryptochirality of saturated quaternary hydrocarbons. The hidden cryptochirality of a nonfunctionalized saturated quaternary asymmetric carbon center, which cannot be distinguished between both enantiomers using any contemporary technique, can be transmitted to a visible chirality using asymmetric autocatalysis. The method of chiral discrimination described above paves the way for studies on the chirality of cryptochiral saturated hydrocarbons, and the above method expands significantly the scope of chiral discrimination of saturated hydrocarbons.

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Supporting Information Available: Additional experimental details and a crystallographic file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) These compounds **5a**−**g** have detectable values of specific rotation.

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